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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,664	08/30/2001	David Botstein	P2548P1C8	2448

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EXAMINER	
O'HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,664	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 20, 2006 has been entered.

Claims Status

2. Claims 27-34 are pending in the instant application.

Withdrawn Objections and Rejections

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 27-34 remain rejected under 35 U.S.C. 101 because the claimed invention is not

supported by either a specific and substantial asserted utility or a well established utility.

Claims 27-34 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The basis for these rejections is set forth at pp. 3-7 of previous Office Action (Paper mailed March 24, 2003), at pp. 3-6 of Paper mailed Sept. 24, 2003, at pp. 3-14 of the Paper Mailed March 17, 2005, Paper mailed Sept. 20, 2005 at pages 3-8, Paper mailed January 24, 2005, and below.

Applicant's arguments (pp. 4-15, Paper filed June 20, 2006) have been fully considered but are not found to be persuasive for the following reasons. Applicant reviews the legal standard for patentable utility, with which the examiner takes no issue.

To review prosecution briefly, the Examiner has made a prima *facie case* that the mild amount of gene amplification (approximately 2 fold to 4 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of protein.

Applicants traverse the rejections and assert that in the response filed November 21, 2005, Applicants submitted declaratory evidence in the form of a Declaration by Paul Polakis, Ph.D., establishing that, in general the correlation between gene amplification and protein expression is art-accepted. Applicants disagree with the advisory action for the reasons maintaining the rejection, and disagree with the advisory action that there is no evidentiary support for Dr. Polakis's statement and disagree with the advisory action that the literature generally cautions against drawing conclusions based on changes in transcript expression levels.

Applicants assert that numerous art references, including the Orntoft, Pollack, Varis, Bermont and Hu references previously submitted and the Papoitti, Walmer, Janssens, Hahnel, Kammori, Maryuamo, Bea and Futcher references submitted herewith establish that generally gene amplification correlates with protein overexpression, and that these references also illustrate that gene amplification in cancerous tissue is an art-accepted indicator of protein overexpression. Finally, although Applicants disagree that explicit data is needed to support the Polakis Declaration, Applicants submit a second declaration of Dr. Polakis, along with data establishing correlation between gene amplification and protein overexpression.

Applicant refers to the second declaration of Dr. Polakis (Polakis II), submitted with the response (filed June 20, 2006) at pg 6-7 of the Response. Applicant argues that this declaration provides the facts, set forth in a table (Exhibits A and B), that more than 90% of the genes identified as being amplified in the Tumor Antigen Project referenced in the Polakis Declarations and in the Gene Amplification Experiment described in Example 28 of the specification, were detectably overexpressed in human tissue compared to normal tissue at both the mRNA and protein levels. More specifically, in his second declaration, Dr. Polakis declares that the data provided therein indicates that "of the 31 genes identified as being detectably overexpressed in human tumor tissue as compared to normal tissue at the mRNA level, 28 of them (greater than 90%) are also detectably overexpressed in human tumor tissue as compared to normal human tissue at the protein level. As such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA."

Applicants assert that this declaratory evidence and data clearly establish that for the claimed polypeptide, one of ordinary skill in art would find it more likely than not that amplification of the PRO357 nucleic acid correlates with overexpression of the PRO357 polypeptide. Applicants further assert that declaratory evidence presented in the Polakis declarations, including Dr. Polakis's statement that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein," is clearly consistent with knowledge in the art. Indeed, the art references discussed below establish that it is more likely than not that one of ordinary skill in the art would accept that qenerallv, there is a correlation between gene amplification and protein overexpression.

The second Polakis declaration under 37 CFR § 1.132 filed June 20, 2006 is insufficient to overcome the rejection of claims 27-34 based upon 25 U.S.C. §§ 101 and 112, first paragraph, for the following reasons. Specifically, data for PRO357 does not appear in the table (Exhibit B). Furthermore, it is not clear how the clones appearing in the table compare to PRO357, or if the results presented in the table were determined by the same methodology as presented in Example 28 of the instant specification. For example, how highly expressed were the genes in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? By what means was the level of mRNA expression determined, e.g., microarray, Northern blot, quantitative PCR? Were matched tissue controls used? The declaration only states that levels of mRNA and protein in tumor tissue were compared to normal tissue.

Applicants discuss the Pollack, Orntoft, Bermont, Varis, Papoitti, Walmer, Janssens, Hahnel, Kammori, Maryuamo, Bea, Futcher and Hu references on pages 7-14 of the response.

Pollack and Varis only teach correlation between gene amplification and mRNA levels, and not correlation between mRNA and protein levels.

With regard to the Orntoft reference, Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one. Applicants' arguments with respect to Orntoft have been fully considered but are not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compare that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO357 in the instant specification. That is, it is not clear whether or not PRO357 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft et al. is not clear.

Applicants present Papoitti, Walmer, Janssens, Hahnel, Kammori, Maryuamo and Bea as supporting their position that overexpression of mRNA correlates with overexpression of protein. All of Applicant's newly cited references with the exception of Futcher et al., are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general.

The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly

larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes (80 proteins examined) and Chen (165 proteins examined) (cited previously by Examiner) and Nagaraja et al. (2006), Waghray et al. (2001) and Sagynaliev et al. (2006) (described below).

Applicant also asserts that Futcher et al. (1999) conducted a study of mRNA and protein expression in yeast and report a good correlation between protein abundance, mRNA abundance, and codon bias. Applicant's arguments have been fully considered but are not found to be persuasive. Futcher et al concludes that "[t]his validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant proteins [emphasis added]" (pg 7368, col 1). Futcher et al. also admits that Gygi et al. performed a similar study and generated similar data, but reached a different conclusion. Futcher et al. indicates that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance" (pg 7367, col 1, 1st full paragraph).

The Examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a change in the mRNA level. Comprehensive studies where significantly large numbers of transcripts and proteins were examined report that increases in mRNA and protein samples are not correlated. Nagaraja et al. (Oncogene, 25:2328-2338, 2006) characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231 and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with

proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*" (see pg 2329, first column). Nagaraja et al. further report that, "a comparative analysis of transcripts and proteins to establish a relationship between transcript changes and protein levels has not yet become routine" (see pg 2328, second column). Lastly, Nagaraja et al. report that, "as dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (see pg 2335, first column).

Similar results were reported by Waghray et al. (Proteomics, 1:1327-1338, 2001). Waghray et al. analyzed gene expression changes induced by dihydrostesterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels (see abstract). In this study, Waghray et al identified transcripts from 16750 genes and found 351 genes were significantly altered by DHT treatment and the RNA level, and identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Out of the 44 protein spots that changed in intensity, Waghray et al. reports that, "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level" (see pg 1333-1334, Table 4). Waghray et al. clearly state that, "The change in intensity for most of the affected proteins identified could not be predicted based on the level of the corresponding RNA" (see abstract).

In a review of gene expression in colorectal cancer (CRC), Sagynaliev et al. (Proteomics, 5:3066-3078, 2005) report that "it is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by

genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (see pg 3068).

In summary, it is clear that Nagaraja, Waghray and Sagynaliev support the Examiner's position that *changes* in mRNA expression frequently do not result in *changes* in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO357. The specification simply discloses a static measurement of PRO357 mRNA in colon tumor as compared to a universal control. There are no teachings in the specification as to the differential expression of PRO357 mRNA in the progression of colon cancer or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicant's measurement of an increase of PRO357 mRNA does not provide a specific and substantial utility for the encoded protein, or an antibody to the protein.

The state of the art, as evidenced through textbooks and review papers, clearly establishes that polypeptide levels cannot be accurately predicted from mRNA levels. Lilley et al. teach that "DNA chips (mRNA profiling studies) can contribute to the study of gene expression in response to a particular biological perturbation. However, the extrapolation that changes in transcript level will also result in corresponding changes in protein amount or activity cannot always be made" ("Proteomics" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, page 351). Wildsmith et al. also disclose that the gene expression data obtained from a microarray may differ from protein expression data ("Gene Expression Analysis Using Microarrays" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, pages 269-286, especially pg 283). King et al. disclose that "it has been established that mRNA levels do not necessarily correlate with protein levels" (pg 2287, 2nd full paragraph). King et al.

state that it has been demonstrated that correlation between mRNA and protein abundance is less than 0.5 and that "mRNA expression studies should be accompanied by analyses at the protein level" (pg 2287, bottom of col 1 through the top of col 2; see also Bork et al., Genome Res 398-400, 2000, especially pg 398, bottom of col 3). Haynes et al. teach that "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks). Madoz-Gurpide et al. disclose that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels" (pg 53, 1st full paragraph).

However, the specification of the instant application has only disclosed that the PRO357 polynucleotide is overexpressed in lung tumor. The specification does not indicate that the PRO357 polypeptide has been overexpressed in the lung tumor sample tested. Given the asserted increase in PRO357 expression, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels. Further research needs to be done to determine whether the purported increase in PRO357 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention

> with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO357 polypeptides have utility in the fields of cancer diagnostics is not substantial.

It is believed that all pertinent arguments have been answered.

Conclusion

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PRIMARY EXAMINER